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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/071,485	02/07/2002	Marie-Ange Buyse	INNS:015--1 11362.0015.DV	8058

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/071,485	BUYSE ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *22-27 and 29-39* is/are allowed.

6)☒ Claim(s) *28 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/485,737.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/7/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group II, claims 22-39 in Paper No. 2/2/04 is acknowledged. Newly added claim 40 will be examined with this group.

Claims 1, 18, 20, 21 are cancelled.

Claims 22-40 are pending and under examination.

Specification

2. The substitute specification filed 2/7/02 has been entered.

3. The disclosure is objected to because of the following informalities:

a. The first line of the specification needs to be updated to indicate 09/485,737 is now US Patent 6,350,860.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 28 is indefinite for reciting "dimerization domain" because the exact meaning of the phrase is not clear. A single chain molecule has an interface where the light and heavy chain dimerize. Is this a dimerization domain?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. The claims 1-21 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line which produces an antibody having the exact chemical identity of D9D10 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the

chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993, IDS 2/7/02)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species D9D10. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Froyen et al (Molecular Immunology 30:805-812, 1993, IDS 2/7/02) and further in view of Queen et al (WO 92/11018, published 7/9/92, IDS 2/7/02) and Pack et al (J. Mol. Biol. 246:28-34, 1995, IDS 2/7/02) and Holliger et al (PNAS 90:6444-6448, 1993).

Claim 40 recites a method for neutralizing interferon-gamma activity in a mammal by administration of a scFv of a humanized D9D10 or a chimeric of D9D10 or a diabody of a humanized D9D10 or a multivalent antibody of a humanized D9D10.

Froyen et al teach a scFv of D9D10 which neutralizes interferon-gamma and the scFv was found to neutralize the antiviral activity and the scFv may have potential use for treatment of diseases. Froyen et al does not teach a humanized scFv or a diabody or a multivalent antibody which is interpreted to be a triabody or tetravalent antibody. Theses deficiencies are made up for in the teachings of Queen et al and Pack et al and Holliger et al.

Queen et al teach methods for humanization of antibodies and antigen binding fragments such as scFv (see page 29, lines 5-15) for treating autoimmune disorders and humanized antibodies specifically for INF-gamma (see page 5, lines 17-28) and methods of producing such.

Holliger et al teach diabodies and the advantages of such.

Pack et al teach triabodies and tetravalent antibodies comprising scFv's.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have combined the teachings of Froyen et al, Queen et al, Pack et al and Holliger for the production of a humanized D9D10 scFv and produce a triabody and a tetravalent antibody for the neutralization of interferon-gamma in a mammal.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success in combining the teachings of Froyen et al, Queen et al, Pack et al, and Holliger et al for the production of a humanized D9D10 scFv and produce a triabody and a tetravalent antibody for neutralizing interferon-gamma because Froyen et al teach "dimeric scFv molecules with higher avidity[] will become of

great importance in the future." (See page 811). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success in combining the teachings of Froyen et al, Queen et al, Pack et al and Holliger et al for the production of a humanized D9D10 scFv and produce a triabody and a tetravalent antibody for neutralizing interferon-gamma because Queen et al teach general methods for the production of humanized antibodies and scFv for the treatment of human autoimmune diseases. Moreover, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success in combining the teachings of Froyen et al, Queen et al, Pack et al and Holliger et al for the production of a humanized D9D10 scFv and produce a triabody and a tetravalent antibody for neutralizing interferon-gamma because Pack et al teach that the miniantibody is useful in the context where extremely high avidity is important or multiple binding is essential yet the molecular weight should remain small. (See page 33). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success in combining the teachings of Froyen et al, Queen et al, Pack et al and Holliger et al for the production of a humanized D9D10 scFv and produce a triabody and a tetravalent antibody for neutralizing interferon-gamma because Holliger et al teach the diabodies represent a class of bivalent antibody fragments similar to Fabs and they should facilitate penetration of tumors and clearance from the serum. Thus, it would have been obvious to humanize the D9D10 scFv and produce a triabody or tetravalent antibody for use in a method to neutralize interferon-gamma in a mammal.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

9. Claims 22-27, 29-39 are in condition for allowance. The prior art does not teach or fairly suggest a method for neutralizing interferon-gamma with an antibody or fragment that binds INFgamma that has a variable domain of amino acids of 1-117 and 133-239 of SEQ ID NO:85.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (571) 272-0871.

11. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is 703-872-9306.

Respectfully,

Larry R. Helms Ph.D.

571-272-0832

LARRY R. HELMS, PH.D
PRIMARY EXAMINER